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TI .alpha.-(3,4-Dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-.alpha.-[(4-methylphenyl)thio]-2(1H)-isoquinolineheptanenitrile (CL 329,753): A novel chemosensitizing agent for P-glycoprotein-mediated resistance with improved biological properties compared with verapamil and cyclosporine A
AU Greenberger, Lee M.; Collins, Karen I.; Annable, Tami; Boni, Joseph P.; May, Michael K.; Lai, Fong M.; Kramer, Robert; Citeralla, Ronald V.; Hallett, William A.; Powell, Dennis
CS Departments Oncology and Immunology, Wyeth-Ayerst Research, Pearl River, NY, 10965, USA
SO Oncology Research (1996), 8(5), 207-218
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LA English
AB Agents that inhibit P-glycoprotein may restore sensitivity to some antitumor drugs in cancer patients. Optimization of the specificity and potency of one class of chemosensitizing agents related to verapamil has led to the identification of CL 329,753. In vitro, 0.1 to 2.0 .mu.M CL 329,753 restored sensitivity to drugs in the multidrug resistance (MDR) phenotype in cell lines that overexpress P-glycoprotein. CL 329,753 was greater than 10-fold more potent and efficacious than cyclosporine A or verapamil in vitro, particularly in cells that express high levels of P-glycoprotein. The enhanced activity of CL 329,753 may be related to its inability to be transported by P-glycoprotein, since low drug accumulation of cyclosporine or verapamil but not CL 329,753 was found in P-glycoprotein-contg. cells, yet all three agents inhibited vinblastine binding to membranes contg. P-glycoprotein and inhibited photoaffinity labeling of P-glycoprotein. In vivo, CL 329,753 resensitized